ABILIFY® (aripiprazole) is the only commercially available partial agonist that modulates both synaptic dopamine and serotonin.*

*Although the mechanism of action of ABILIFY* (aripiprazole) is unknown, the efficacy of ABILIFY could be mediated through a combination of partial agonist activity at the dopamine D₃ and serotonin 5HT₁A receptors, and antagonist activity at the serotonin 5HT₂A receptors. Actions at receptors other than D₃, 5-HT₁A, and 5-HT₂A may explain some of the other clinical effects of aripiprazole (eg, the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic alpha₁ receptors).

**Indication**

ABILIFY is indicated for:

- Use as an adjunctive therapy to antidepressants in adults with Major Depressive Disorder who have had an inadequate response to antidepressant therapy
- Acute and maintenance treatment of manic or mixed episodes associated with Bipolar I Disorder as monotherapy and as an adjunct to lithium or valproate in adults

**Suicidality and Antidepressant Drugs**

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of adjunctive ABILIFY or another antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increased risk of suicidality in adults beyond age 24. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ABILIFY is not approved for use in pediatric patients with depression.

Please see IMPORTANT SAFETY INFORMATION, including Boxed WARNINGS, and INDICATIONS, for ABILIFY on pages 4 and 5.
ABILIFY® (aripiprazole) is a partial agonist at both dopamine and serotonin receptors.

**Receptor Activity**

<table>
<thead>
<tr>
<th>Receptor System</th>
<th>Dopamine</th>
<th>Serotonin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neureceptor Subtype/Action</td>
<td>D₂ partial agonist</td>
<td>5-HT₁₆ partial agonist</td>
</tr>
<tr>
<td></td>
<td>D₃ partial agonist</td>
<td>5-HT₂₆ antagonist</td>
</tr>
</tbody>
</table>

*Although the mechanism of action of ABILIFY is unknown, the efficacy of ABILIFY could be mediated through a combination of partial agonist activity at the dopamine D₂ and serotonin 5HT₁₆ receptors, and antagonist activity at the serotonin 5HT₂₆ receptors.

†Based on preclinical data.

‡Data with cloned human receptors.

**Theoretical action of partial agonist compared to full agonist and antagonist**

![Graph showing theoretical action of partial agonist compared to full agonist and antagonist](image)

A partial agonist may have the same potency as a full agonist, but at a lower maximal level of response.

**Indication**

ABILIFY is indicated for use as an adjunctive therapy to antidepressants in adults with Major Depressive Disorder who have had an inadequate response to antidepressant therapy.

**Contraindication**

Known hypersensitivity reaction to ABILIFY. Reactions have ranged from pruritus/urticaria to anaphylaxis.
Modulating dopaminergic and serotonergic activity sets ABILIFY® (aripiprazole) apart²*

Help modulate dopamine and serotonin activity with ABILIFY

ABILIFY is thought to partially activate dopamine and serotonin receptors, thereby modulating neuronal activity in both hypoactive and hyperactive environments³

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). Although the causes of death were varied, most of the deaths appeared to be cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

Important Warning and Precaution for Cerebrovascular Adverse Events, Including Stroke
Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with ABILIFY.

Please see IMPORTANT SAFETY INFORMATION, including Boxed WARNINGS, and INDICATIONS, for ABILIFY on pages 4 and 5.
INDICATIONS
ABILIFY is indicated for:
- Use as an adjunctive therapy to antidepressants in adults with Major Depressive Disorder who have had an inadequate response to antidepressant therapy
- Acute treatment of manic or mixed episodes associated with Bipolar I Disorder as monotherapy and as an adjunct to lithium or valproate in adults
- Maintenance treatment of Bipolar I Disorder, both as monotherapy and as an adjunct to lithium or valproate in adults

IMPORTANT SAFETY INFORMATION
Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). Although the causes of death were varied, most of the deaths appeared to be cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of antidepressive ABILIFY or another antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increased risk of suicidality in adults beyond age 24. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ABILIFY is not approved for use in pediatric patients with depression.

See Full Prescribing Information for complete Boxed WARNINGS

Contraindications – Known hypersensitivity reaction to ABILIFY. Reactions have ranged from pruritus/urticaria to anaphylaxis.

Cerebrovascular Adverse Events, Including Stroke – Increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with ABILIFY

- Neuroleptic Malignant Syndrome (NMS) – As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with ABILIFY. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems

Tardive Dyskinesia (TD) – The risk of developing TD and the potential for it to become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing should be consistent with the need to minimize TD. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn

Metabolic Changes – Atypical antipsychotic drugs have been associated with metabolic changes that include:
- Hyperglycemia/Diabetes Mellitus – Hyperglycemia, in some cases extreme and associated with ketaodiosis, coma, or death, has been reported in patients treated with atypical antipsychotics including ABILIFY. Patients with diabetes should be regularly monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug
- Dyslipidemia – Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. There were no significant differences between ABILIFY- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting LDLs, and fasting/nonfasting HDLs
- Weight Gain – Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended

Orthostatic Hypotension – ABILIFY may be associated with orthostatic hypotension and should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.
Commonly observed adverse reactions (>5% incidence and at least twice the rate of placebo for ABILIFY vs placebo, respectively):

- Adult patients with Major Depressive Disorder (adjunctive treatment to antidepressant therapy): akathisia (25% vs 4%), restlessness (12% vs 2%), insomnia (8% vs 2%), constipation (5% vs 2%), fatigue (8% vs 4%), and blurred vision (6% vs 1%)
- Adult patients (monotherapy) with Bipolar Mania: akathisia (13% vs 4%), sedation (8% vs 3%), tremor (6% vs 3%), restlessness (6% vs 3%), and extrapyramidal disorder (5% vs 2%)
- Adult patients (adjunctive therapy with lithium or valproate) with Bipolar Mania: akathisia (19% vs 5%), insomnia (8% vs 4%), and extrapyramidal disorder (5% vs 1%)

Dystonia is a class effect of antipsychotic drugs. Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Pregnancy: Non-Teratogenic Effects – Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. These complications have varied in severity; from being self-limited to requiring intensive care and prolonged hospitalization. ABILIFY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers – ABILIFY is excreted in human breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Please see accompanying FULL PRESCRIBING INFORMATION, including Boxed WARNINGS, for ABILIFY in pocket.

ABILIFY® (aripiprazole) apart*

- Is thought to increase neuronal activity in hypoactive conditions³
- Is thought to decrease neuronal activity in hyperactive conditions³
- Has a high affinity for both dopamine and serotonin receptors
- Functions as a partial agonist at the dopamine D₃, D₅, and the serotonin 5-HT₁₆ receptors, and as an antagonist at the serotonin 5-HT₁₅ receptor

The mean elimination half-lives of aripiprazole and dehydro-aripiprazole are 75 hours and 94 hours, respectively.

*Although the mechanism of action of ABILIFY is unknown, the efficacy of ABILIFY could be mediated through a combination of partial agonist activity at the dopamine D₃ and serotonin 5HT₁₆ receptors, and antagonist activity at the serotonin 5HT₁₅ receptors.

Important Warning and Precaution for Neuroleptic Malignant Syndrome (NMS)
As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with ABILIFY. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems.

Please see IMPORTANT SAFETY INFORMATION, including Boxed WARNINGS, and INDICATIONS, for ABILIFY on pages 4 and 5.